UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/499,875	02/08/00	GRIFFEY R	IBIS-0261

HM12/0925

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EXAMINER	
PRASTHOFER, T	
ART UNIT	**PAPER NUMBER**
1627	10

DATE MAILED: 09/25/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary file copy	Application No. 09/499,875	Applicant(s) GRIFFEY ET AL.	
	Examin r Thomas W Prasthofer	Art Unit 1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-120* is/are pending in the application.

4a) Of the above claim(s) *1-29 and 47-120* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

Change of Examiner

The examiner of this application has changed from Barba Koroma to Thomas Prasthofer.

Status of the Application

Receipt is acknowledged of a reply to a restriction requirement on July 9, 2001 in Paper No. 9.

Response to Restriction and Election of Species with Traverse

Applicant's election with traverse of Group II, claims 30-46 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the inventions of groups I-XIII are not independent and that the subject matter of the groups is not divergent and would therefore not pose a burden to search simultaneously.

This is not found persuasive because MPEP 803 states that restriction is proper when the inventions are independent **or** distinct **and** there is a serious burden on the examiner. The inventions of groups I-XIII are distinct inventions for the reasons stated in Paper No. 5. Examiner does not agree that the subject matter of the different groups is not divergent. There are different reagents, conditions, and outcomes specified in the independent claims and the dependent claims associated with each of the independent claims amplify the divergence of literature, computer, and classification searches required for the different groups. Searching the groups as outlined by applicant in Paper No. 9 would pose a serious search burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Status of the Claims

Claims 1-120 are pending in the present application. Claims 1-29 and 47-120 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

Claims 30-46 are being examined on their merits.

Objections to the Claims

1. In claim 30 there is a minor typographical error; "a" is missing in the first line between "of" and "group."

2. It appears that there is a typographical error in claim 37 ("completes" vs. "complexes").

Claims Rejections – 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 30-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The use of a standard compound as a binding partner to a target molecule that can be displaced by a (test) compound is not enabled by the specification. The use of ammonium ion as a standard ligand and/or RNA as a target using the claimed method is not enabled by the

specification. Practicing the presently claimed method would require undue experimentation on the part of one wishing to use the claimed invention.

Several factors are to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any required experimentation is "undue." These factors include:

1) the breadth of the claims
2) the nature of the invention
3) the state of the prior art
4) the level of one of ordinary skill
5) the level of predictability in the art
6) the amount of direction provided by the inventor
7) the existence of working examples
8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In the present case, the claims encompass any target molecule, any "standard compound" and any group of (test) compounds whatsoever. The state of the prior art was such that known ligands known to bind to specific sites on a target molecule could be used as "standard compounds" and that their displacement from a target molecule by a test compound with higher affinity for that specific site on the molecule could be detected and quantified by mass spectrometry. The predictability of detecting the binding of a test compound to a target molecule by the displacement of a "standard compound" with no limitation that the test and "standard" compounds bind the same sites on the target molecule is very low, particularly with larger target molecules and smaller test molecules. The inventor provides no working example to exemplify the use of the claimed method. The specification provides only general guidance with respect to selection of "standard" compounds (e.g. the use of ammonium ion or amine-containing standard ligands) and provides insufficient guidance with respect selecting different types of "standard" compounds for use with different types of target molecules or how to select "standard" compounds that are detectable by mass spectrometry and able to bind a target molecule. The specification appears to direct one of ordinary skill in the art to use non-specific "standard" compounds which may or may not bind the target molecule of interest and may or may not bind

at a site on the target that is of interest to one using the invention. Substantial experimentation would be required to determine what "standard" compounds (in what amounts) can be used (selected) with a particular target molecule that simultaneously satisfy the requirements for detection by mass spectrometry, binding affinity, and binding to the site of interest on the target molecule, for example.

Claims Rejections – 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are:

A) The "standard compound" that forms a non-covalent complex with the target of interest must bind to the same site on a target molecule as those members of a group of compounds that can form a non-covalent complex with a target molecule. Alternatively there must be some causative relationship between the binding of (test) compounds to a target molecule and the displacement of the "standard compound." If both the (test) compound and the "standard" compound can bind simultaneously and independently to a target molecule the method would appear to be inoperative.

B) The cooperative relationships between "affinity," "signals," "signal strength," and "background noise" are omitted.

5. Claims 30 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 30, it is not clear what a "baseline affinity" is because the relationship between "affinity," "signals," "signal strength," and "background noise" are not clear.

B. In claim 30, it is not clear what is meant by "background noise." It is not possible for one of ordinary skill in the art to determine the metes and bounds of the term.

C. The term "diverse compounds" in claims 33 and 25 is a relative term which renders the claim indefinite. The term "diverse" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. One of ordinary skill in the art would not be able to determine the metes and bounds of the compounds encompassed by the claim.

D. The term "related compounds" in claim 34 is a relative term which renders the claim indefinite. The term "related" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. One of ordinary skill in the art would not be able to determine the metes and bounds of the compounds encompassed by the claim or how compounds are to be "related".

E. In claim 34 it is not clear what the meaning of the term "historical repository of compounds" is or how one would determine the metes and bounds of compounds encompassed by the term.

F. In claim 40 it appears that, if one of the "members of said group of compounds" has no more than one sulfur, phosphorous, or halogen atom, that member may have more than 4 rotatable bonds and/or a molecular weight of more than about 200 Daltons. The claim language is not entirely clear. Clarification is required.

G. In claim 45 it is not clear if "ammonium" is intended to be "ammonium ion" or if it is intended to be a molecule containing an ammonium group. Clarification is required.

Claims Rejections – 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 30-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. J. Am. Chem. Soc. (1995) 117:8859-8860, Lim et al. J. Mass Spectrometry (1995) 30:708-714, and Loo, J.A. Mass Spectrometry Reviews (1997) 16:1-23.

The Cheng et al. reference teaches the study of the competitive binding of various inhibitors of carbonic anhydrase using ESI-FTICR-MS (page 8859, column 1). Mixtures of inhibitors were introduced into a mass spectrometer and the relative abundances of the resulting complex ions were determined. The benzesulfonamides inhibitors used have molecular weights of less than about 600 Daltons and fewer than 8 rotatable bonds (see, for example, figure 2).

The Cheng et al reference does not explicitly teach the use of a "standard compound," adjusting the operating performance to provide a particular ratio of bound and unbound target molecule with the standard compound, or including the standard compound with a mixture of ligands into a mass spectrometer. The Cheng et al. reference does not explicitly teach storing the relative abundance and stoichiometry of ligand-target complexes in a relational database with cross referencing, RNA target molecules, or ligands with fewer than 4 rotatable bonds and molecular weights of less than about 200 Daltons.

The Lim et al. reference teaches a method for determining the binding constants of vancomycin and ristocetin for components of bacterial cell walls. Callibration curves with ammonium acetate (standard compound) for bacterial cell wall components (targets) were determined. Ammonium acetate was also present in the mixtures of either vancomycin or ristocetin with their targets.

The Loo reference teaches the study of protein-RN complexes by ESI-MS (table 1).

It would have been obvious to one of ordinary skill in the art to alter the design of the Cheng et al method to include a "standard compound" at the time that the invention was made. One would have been motivated to do so to have an internal positive (or negative) control and/or to make a comparison between a known ligand and unknown ligands in the screening of, for example, lead molecules for drug discovery. One would have had reasonable expectation for success because competitive binding assays were routine in the art at the time that the invention was made and Loo suggests using positive and negative controls as well as the screening of lead molecules for drug discovery on pages 15 and 14.

Once a standard compound was selected, adjustments to the operating performance including voltage across a desolvation capillary, lens element, and signal strength would have been well within the abilities of one of ordinary skill to select as a matter of design choice. Similarly, the selection of a target molecule and libraries of compounds (number f compounds and molecular weights/rotatable bonds) would have been well within the abilities of one of ordinary skill in the art to select. RNA, proteins, DNA etc. were all conventional ligand-binding targets in drug research at the time.

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to store the resulting data in a cross referenced relational database. One would have motivated to do so because the storage of binding data in relational databases was routine at the time. Selecting a particular affinity between the test compound and target molecule (within the range of biologically relevant dissociation constants such as 50 mM) would also have been well within the abilities of one of ordinary skill.

7. Claims 30-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao et al. J. Med. Chem. (1996) 39:1949-1955 and Loo, J.A. Mass Spectrometry Reviews (1997) 16:1-23.

The Gao et al. reference teaches the use of electrospray ionization-mass spectrometry to screen libraries of carbonic anhydrase inhibitors (abstract). Ammonium acetate (standard compound) was used alone with carbonic anhydrase and produced charge states of +/- 7 (page 1950, column 1). Libraries were screened in the presence of ammonium acetate (ammonium) and the resulting mass spectra were used to determine relative binding affinities based on ion intensities (relative ion abundance) and molecular weights. The collections molecules used (drug substances) were both diverse and related because all of the structures were derived from 4-carboxybenzene-sulfonate (related) but contained different amino acids in both the D- and L-configurations (diverse) (see, for example, figure 2). These molecules have molecular weights of less than about 600 Daltons and fewer than 8 rotatable bonds. The adjustment of desolvation capillary temperature (via Watts supplied to a resistor) is taught on page 1953 at the bottom of the second column.

The Gao et al. reference does not explicitly teach using subsets of 2 to 8 ligand compounds, adjusting the signal strength to a particular range of values, the storage of results in

cross-references relational databases, RNA as a target molecule, particular adjustments to a lense element, or ligands (compounds) with molecular weights of less than about 200 Daltons with fewer than 4 rotatable bonds.

The Loo reference teaches the study of protein-RN complexes by ESI-MS (table 1).

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to use molecules other than enzymes such as RNA as target molecules, to use compounds with molecular weights of less than about 200 Daltons with fewer than 4 rotatable bonds, and to store the results in across-referenced relational database. One would have been motivated to do so because numerous RNA drug targets and associated ligands including those with molecular weights of less than about 200 Daltons were known in the art at the time that the invention was made See Loo et al. table 1). The storage of data from large scale screening of drug candidates was routine in the art at the time that the invention was made. Adjustments to the operating parameters of the instruments was well within the abilities of one of ordinary skill in the art at the time that the invention was made. Selecting a particular affinity between the test compound and target molecule (within the range of biologically relevant dissociation constants such as 50 mM) would also have been well within the abilities of one of ordinary skill.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas Prasthofer** at telephone number **(703) 308-4548**. The examiner can normally be reached on Monday, Tuesday, Friday, and Saturday 8:00-6:30.

9. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-2742.

10. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist at (703) 308-1235.

Thomas Prasthofer, Ph.D.
September 24, 2001

DR. JYOTHSNA VENKAT PH.D
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